UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,877	12/09/2003	Jill A. O'Loughlin	B0877.70025US00	9392

7590 01/25/2006

Tani Chen, Sc.D.
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,877	O'LOUGHLIN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-9,17-24,40,44-46,62,66,67 and 86-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-9,17-24,40,44-46,62,66,67 and 86-93* is/are rejected.

7)☒ Claim(s) *1,40,62 and 86* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Applicant's Request for Continued Examination filed 01 December 2005 has been received and entered into the case. Claims 3, 4, 10-16, 25-39, 41-43, 47-61, 63-65, 68-85, and 94-98 have been cancelled. Claims 1, 2, 5-9, 17-24, 40, 44-46, 62, 66, 67 and 86-93 remain pending, all of which have been considered on the merits. All arguments have been fully considered.

Claim Objections

Claim 1 is objected to because, while not so unclear so as to render the claim indefinite, the wording of the claim is slightly confusing, particularly with regards to the preamble. It is suggested that claim 1 be changed to: "An oral delivery composition comprising a capsule and a pharmaceutically acceptable carrier, wherein the capsule comprises each of isolated uricase and isolate creatininase."

Similarly, it is suggested the language of claim 40 be altered to make the preamble more clear: "An oral delivery composition comprising a capsule and a pharmaceutically acceptable carrier, wherein the capsule comprises at least one cell transfected with both a uricase gene and a creatininase gene."

Similarly, it is suggested the language of claim 62 be altered to make the preamble more clear: "An oral delivery composition comprising a capsule and a pharmaceutically acceptable carrier, wherein the capsule comprises at least one cell transfected with each of a urease gene, a uricase gene, and a creatininase gene, and wherein the at least one cell is not *E. coli*."

Similarly, it is suggested the language of claim 86 be altered to make the preamble more clear: "An oral delivery composition comprising a capsule, wherein the capsule comprises at least two different types of isolated uremic enzymes."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-9, 17-21, 86-91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al (Int J. Artif. Org, 1987), in view of Ranganathan et al (US 2001/0051150 A1), and in light of The Online Medical Dictionary and IUBMB Enzyme Nomenclature.

Wolfe et al teach an article comprising an oral delivery composition comprising a capsule, the capsule comprising isolated urease dissolved in a 10% haemoglobin solution (which applicant calls a pharmaceutically acceptable carrier) and a zirconium phosphate material (an ammonium uptake species) (See Wolfe et al, Pg. 269, col. 2-Pg. 270, col. 1) (Claims 2, 18-21, 88 & 92). Wolfe et al does not include any whole cells in their composition (Claim 17). Wolfe et al teach that the urease successfully breaks down urea in gut fluid, and the zirconium phosphate helps to absorb ammonium produced as a bi-product of the urea breakdown (See Wolfe et al, abstract). Wolfe et al teach the orally ingestible article is intended to remove urea in patients with kidney failure in order to delay the need of dialysis therapy or to reduce dialysis treatment times (See Wolfe et al, abstract).

Wolfe et al only teaches inclusion of urease enzymes for breakdown of urea in patients with kidney failure; however it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally include appropriate enzymes for the enzymatic breakdown of additional toxins known to build up in patients with kidney failure, specifically uricase and creatininase, for the breakdown of uric acid and creatinine, respectively (See Online Medical Dictionary "Uricase" and IUBMB Enzyme Nomenclature "EC 3.5.2.10") (Claims 1, 86, 87, 89, and 90). At the time the invention was made it was well known that several nitrogenous wastes build up in the systems of kidney failure

patients, most notably urea, uric acid and creatinine (See Ranganathan et al, Pg. 1, paragraph 0005 & Pg. 2, paragraph 0012). For the most effective treatment all three of the nitrogenous wastes should be removed from the intestines of the individual (See Ranganathan et al, Pg. 2 paragraph 0012). One of ordinary skill in the art would have been motivated to include isolated uricase and creatininase in the microcapsules of Wolfe et al, along with the urease, for the effective breakdown of uric acid, and creatinine and urea, respectively, in a patient suffering renal failure because the most effective treatment requires removal of all three toxins present in elevated concentrations in the gastrointestinal tract of such patients (See Ranganathan et al, Pg. 1, paragraph 0005). One would expect success including isolated uricase and creatininase in the microcapsules of Wolfe et al because uricase and creatininase are both commercially available, and one would not expect negative interactions between the three enzymes within the microcapsule; rather one would have a reasonable expectation that the uricase and creatininase would function similarly to the urease by breaking down their respective toxins.

Additionally, though Wolfe et al teach the urease enzymes are encapsulated, they are relatively silent on the specifics of the actual capsule. However, Ranganathan et al teach a microcapsule carrier for oral ingestion wherein the actual microcapsule can be designed to be insusceptible to acid degradation, so that the contents of the capsule are not substantially released externally from the capsule, can be enterically coated, and wherein the capsule does not impede mass transport of uric acid or creatinine through the capsule; material suitable for such microcapsules include alginate (See Ranganathan et al, Pgs. 2-3, paragraph 0020). Therefore, at the time the invention was made it would have been well within the purview of one of ordinary skill in the art to use a capsule material, such as that described by Ranganathan et al, in the microcapsules of Wolfe et al, modified to additionally contain isolated uricase and creatininase enzymes (Claims 5-9, 91 and 93). One of ordinary skill in the art would have been motivated to use a microcapsule such as that described by Ranganathan et al, to encapsulate the enzymes of Wolfe et al, in order to protect the urease from proteolytic enzymes in the gut (See Wolfe et al, Pg.

269, col. 2), to ensure the article is delivered to the intestines, where maximal degradation of the urea is to occur, as opposed to being degraded in the acidic stomach environment, and in order to contain the active enzymes in a protected capsule where they are protected from binding of other macromolecules present in the gut that may inhibit the enzymatic action. One would expect success using the microcapsule of Ranganathan et al because Ranganathan et al teach their microcapsules can successfully be ingested and are delivered to the intestines of the individual without substantially being degraded by acid or releasing their contents externally of the capsule (See Ranganathan et al, Pg. 3, paragraph 0020). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 18-24 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al (Int J. Artif. Org, 1987), in view of Ranganathan et al (US 2001/0051150 A1), and further in view of Kominami et al (US Patent 4,240,376), Sparks et al (Trans Am. Soc. Artif. Int Organs, 1972) and Smith et al (US Patent 4,857,555).

Wolfe et al teach an article comprising an oral delivery composition comprising a capsule, the capsule comprising isolated urease dissolved in a 10% haemoglobin solution (which applicant calls a pharmaceutically acceptable carrier) and a zirconium phosphate material (an ammonium uptake species) (See Wolfe et al, Pg. 269, col. 2-Pg. 270, col. 1). Wolfe et al teach that the urease successfully breaks down urea in gut fluid, and the zirconium phosphate helps to absorb ammonium produced as a bi-product of the urea breakdown (See Wolfe et al, abstract). Though Wolfe et al only includes urease in their composition, it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally include isolated creatininase and uricase, see teachings above.

Wolfe et al does teach inclusion of a zirconium phosphate as an ammonium uptake species; however, it would have been obvious to one of ordinary skill in the art to alternatively use activated carbon (See Kominami et al, col. 5, ln 51-66) or oxidized starch (which applicant calls oxystarch) (See

Sparks et al, Pg. 459) (Claims 18-21 & 92). Like Wolfe et al, Kominami et al and Sparks et al have all shown activated carbon and oxidized starch to be suitable sorbents for the adsorption of ammonia, which is formed by the breakdown of urea by urease. Therefore one of ordinary skill in the art would have been motivated to alternatively use activated carbon or oxidized starch in place of the zirconium phosphate as the ammonium uptake species, and would have expected success in doing so, as they are functional equivalents.

Other known ammonium uptake species include a glutamine synthetase. Smith et al teach that glutamine synthetase is responsible for catalyzing the synthesis of glutamine from glutamate and ammonia (See Smith et al, col. 1, ln 34-50); the glutamine produced by this reaction is readily used by the body in a variety of natural ways. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively include glutamine synthetase in the modified microcapsule of Wolfe et al in place of the zirconium phosphate (Claims 22-24 and 92). One would have been motivated to substitute glutamine synthetase in the modified microcapsule of Wolfe et al in place of the zirconium phosphate as the ammonium uptake species as they are functional equivalents. One would have expected success because Smith et al teach that glutamine synthetase catalyzes the reaction of glutamate and ammonia to form glutamine, which can then forth be utilized directly in the gastrointestinal tract as respiratory fuel (See Smith et al, col. 1, ln 34-col. 2, ln 2).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 40, 44, 45, 62, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Ranganathan et al (US 2001/0051150 A1), Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562) and in light of The Online Medical Dictionary & IUBMB Enzyme Nomenclature.

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln 24-31). The microencapsulating material can be an alginate-polylysine-alginate (which applicant calls a pharmaceutically acceptable carrier) (See Chang et al, col. 2, ln 38-45). The microencapsulating material is able to entrap the microorganisms so that the microorganisms are not released externally from the capsule, but does not impede mass transport of the undesirable molecules for removal to enter in contact with the entrapped microorganisms (See Chang et al, col. 2, ln 46-52) (Claims 45 & 66).

In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See Chang et al, col. 3, ln 58- col. 4, ln 40 & Claim 9).

At the time the invention was made it was known that urea, creatinine and uric acid are all present in the small intestines of uremic patients, each in sufficient quantities that require removal for effective treatment of the renal failure associated with uremia (See Ranganathan et al, Pg. 1, paragraph 0005 & page 2, paragraph 0012). While the article of Chang et al includes a cell transfected with the urease gene, for the purpose of removing urea from the gastrointestinal tract of uremic patients, it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally transfect the cell with the uricase and creatininase genes so that the encapsulated cell also produces uricase and creatininase, for the breakdown of uric acid and creatininase, as well (See Online Medical Dictionary "Uricase" and IUBMB Enzyme Nomenclature "EC 3.5.2.10"). One of ordinary skill in the art would have been motivated to use cells transfected with each of the uricase, creatininase and urease genes so the cell would produce uricase, creatininase and urease for the effective breakdown of uric acid, creatinine and urea, respectively, in a uremic patient, which were all known to be present, in elevated

concentrations, in the gastrointestinal tract of uremic patients (See Ranganathan et al, Pg. 1, paragraph 0005) (Claims 40 & 44).

Chang et al has shown that oral delivery of microorganisms expressing urease successfully decreases urea levels in uremic patients (See Chang et al, col. 9, ln 59-col. 10, ln 15). One would expect expression of creatininase and uricase in the gastrointestinal tract (by the encapsulated, transfected microorganisms) would also result in successful decrease of creatinine and uric acid toxins in uremic patients. Therefore one would expect that these toxins, present in the GI tract, could be successfully broken down by the enzymes present in the GI tract (via oral delivery of the encapsulated, transfected microorganisms). Regarding transfection of the microorganisms with the creatininase and uricase genes, it was known at the time the invention was made how to transfect microorganisms, including *E.coli* with the creatininase and uricase genes. For example Shigyo et al teach isolation of the uricase gene from Bacillus sp. and subsequent transfection into and expression in *E.coli* cells (See Shigyo et al, col. 6, ln 15-col. 8, ln 34). Additionally, Yamamoto et al teach isolation of the creatininase gene from *Pseudomonas putida* PS-7 and subsequent transfection into and expression in *E.coli* cells (See Yamamoto et al, col. 3, ln 6-57 & Claim 5). Therefore, one would have expected success modifying the oral delivery article of Chang et al to comprise a microorganism transfected with the urease, uricase, and creatininase genes.

Alternatively, though Chang et al, Shigyo et al and Yamamoto et al teach examples wherein the urease, uricase and creatininase genes, respectively, are transfected into *E.coli* cells it would have been obvious to one of ordinary skill in the art to use any suitable microorganism as the host cell in which to transfect the three genes of interest (Claim 62). The choice of host microorganism would have been a matter of experimental design choice; any suitable, biocompatible bacteria that can easily be genetically engineered would have been suitable. One of ordinary skill in the art would have been motivated to use any suitable microorganism because Chang et al teach that any suitable microorganism can be used in accordance with their invention, including, for example, *Bacillus pastteuri* (See Chang et al col. 3, ln 58-

65). One would have expected success because one of ordinary skill in the art would be able to select a microorganism suitable for transfection and in vivo use, as methods of transfection are well known in the art (See, e.g. Shigyo et al and Yamamoto et al), and Chang et al teach a general method of encapsulation that is applicable to multiple cell types. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 46 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (US Patent 6,217,859), in view of Ranganathan et al (US Patent 6,706,263), Yamamoto et al (US Patent 5,627,065) and Shigyo et al (US Patent 5,728,562), further in view of Sparks et al (Trans. Amer. Soc. Artif. Int. Organs, 1972), Wolfe et al (The International Journal of Artificial Organs, 1987) and Kominami et al (US Patent 4,240,376).

Chang et al teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier (which applicant calls a capsule comprising at least one cell transfected with a gene) (See Chang et al, col. 2, ln 24-31). In a preferred embodiment Chang et al teach encapsulating genetically engineered *E.coli* DH5 cells, which are transfected with the urease gene from *Klebsiella aerogens*, for the purpose of urea removal (See col. 3, ln 58- col. 4, ln 40 & Claim 9).

It would have been obvious for the oral delivery composition of Chang et al to comprise a cell that is additionally transfected with the uricase and creatininase genes in addition to the urease gene, as taught above. Though Chang et al uses an *E.coli* cell, it would have been obvious to use a cell that is not *E. coli*, as taught above.

Chang et al does not teach including an ammonium uptake species in the capsule; however, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include an ammonium uptake species in the capsules. Such ammonium uptake species include zirconium

phosphate (See Kominami et al, col. 5, ln 51-66 & Wolfe et al, Pg. 269), activated carbon (See Kominami et al, col. 5, ln 51-66) and oxidized starch (which applicant calls oxystarch) (See Sparks et al, Pg. 459) (Claims 46 and 67). Kominami et al, Wolfe et al and Sparks et al have all shown zirconium phosphate, activated carbon and oxidized starch to be suitable sorbents for the adsorption of ammonia, which is formed by the breakdown of urea by urease (See The Online Medical Dictionary, "Urease"). Therefore one of ordinary skill in the art would have been motivated to include at least one of zirconium phosphate, activated carbon and oxidized starch in the modified microcapsules of Chang et al in order to adsorb the excess ammonia created by the breakdown of urea. One would have expected success because zirconium phosphate, activated carbon and oxidized starch are all taught to adsorb ammonia (See Kominami et al, Wolfe et al and Sparks et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments with respect to claims 1 and 86, and dependent claims thereof, have been considered but are moot in view of the new ground(s) of rejection over Wolfe et al, in view of Ranganathan et al.

Applicant's arguments with respect to claims 40 and 62, and dependent claims thereof, have been fully considered, but are not found persuasive. The rejection over these claims has been modified to incorporate the teachings of Ranganathan et al.

Applicant has argued that neither Chang et al nor Setala et al teach or suggest transfecting a cell with either uricase gene or creatininase gene, and therefore certainly do not teach or suggest transfecting a cell with both of those genes, as required by the current claims. Applicant argues there was no motivation to transfect the cell of Chang et al with genes for uricase and/or creatininase, because it was not known at the time the invention was made whether uric acid and creatinine were each present in the intestine at

concentrations which would make their removal therapeutically useful. Applicants feel the passage in Setala et al, relied upon by the examiner, does not teach the presence of uric acid and creatinine specifically in the intestines, where the claimed article would be active; therefore applicants argue there would be no expectation of successfully combining the cited references for the purposes stated in the rejection.

Applicant's arguments have been considered, and while the examiner does not concede that the passage in Setala et al does not provide evidence of uric acid and creatinine in the intestines of a uremic patient, newly cited Ranganathan et al more clearly states that all three of urea, uric acid and creatinine, are present in abnormal levels in the gastrointestinal tract of a patient with renal failure, and provides motivation to remove uric acid and creatinine, in addition to urea, from the system in order to provide the most effective treatment (See Ranganathan et al, Pg. 1, paragraph 0005 and Pg. 2, paragraph 0012). Therefore, the examiner maintains, that in view of the clear teachings of Ranganathan et al on the presence of urea, uric acid and creatinine in the GI tract of uremic patients, one of ordinary skill in the art would have been motivated to modify the article of Chang et al to include cells transfected with genes for all three of urease, uricase, and creatininase, for the removal of urea, uric acid and creatinine from a patient's GI tract for the most effective treatment.

Applicant's arguments directed towards dependent claims 44-46 and 66-67 were based on the same arguments presented for the independent claims, wherein the additional references relied upon failed to cure the deficiencies of the primary references. The arguments regarding the rejection of independent claims 40 and 62 have been addressed above. With no additional arguments pertaining to the specific rejections of the limitations of claims 44-46, 66, or 67, the rejections stand for the reasons of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER